PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 19 January 2000 (19.01.00)	
International application No. PCT/CA99/00571	**Applicant's or agent's file reference** 1770-206PCT
International filing date (day/month/year) 17 June 1999 (17.06.99)	**Priority date** (day/month/year) 19 June 1998 (19.06.98)
Applicant DAMHA, Massad, José et al	

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:

   08 December 1999 (08.12.99)

   [ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

   [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 G neva 20, Switzerland	Authorized fficer Olivia RANAIVOJAONA
Facsimile N .: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

3059120

WO 99/67378
PCT/CA99/00571

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

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NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
COTE, France
Swabey Ogilvy Renault
Suite 1600
1981 McGill College Avenue
Montréal, Québec H3A 2Y3
CANADA

Date of mailing (day/month/year) 29 December 1999 (29.12.99)	
Applicant's or agent's file reference 1770-206PCT	**IMPORTANT NOTICE**
International application No. PCT/CA99/00571	**International filing date** (day/month/year) 17 June 1999 (17.06.99)
Priority date (day/month/year) 19 June 1998 (19.06.98)	
Applicant McGILL UNIVERSITY et al	

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,CN,EP,IL,JP,KP,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CU,CZ,DE,DK,EA,EE,ES,FI,GB,GD,GE,GH,GM,HR,
   HU,ID,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,OA,PL,PT,RO,RU,
   SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,UA,UG,UZ,VN,YU,ZA,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   29 December 1999 (29.12.99) under No. WO 99/67378

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra

Telephone No. (41-22) 338.83.38

Continuation of Form PCT/IB/308

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

Date of mailing (day/month/year)	IMPORTANT NOTICE
29 December 1999 (29.12.99)	
Applicant's or agent's file reference	**International application No.**
1770-206PCT	PCT/CA99/00571

The applicant is hereby notified that, at the time of establishment of this Notice, the time limit under Rule 46.1 for making amendments under Article 19 has not yet expired and the International Bureau had received neither such amendments nor a declaration that the applicant does not wish to make amendments.

PATENT COOPERATION TREATY

REC'D 21 SEP 2000
WIPO PCT

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

15

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
1770-206PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA99/00571	17/06/1999	19/06/1998
International Patent Classification (IPC) or national classification and IPC C12N15/11		
Applicant McGILL UNIVERSITY et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 12 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which hav been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 14 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☒ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
08/12/1999	15.09.00
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Moonen, P Telephone No. +49 89 2399 8538

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

Int mational application No. PCT/CA99/00571

I. Basis f the r p rt

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-53	as originally filed			

Claims, No.:

1-20	as received on	20/04/2000	with letter of	20/04/2000
21-30	as received on	29/08/2000	with letter of	21/08/2000

Drawings, sheets:

1/16-16/16	as originally filed

2. The amendments have resulted in the cancellation of:

☐	the description,	pages:	
☒	the claims,	Nos.:	25,29-30
☐	the drawings,	sheets:	

3. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

see separate sheet

4. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   ☐ copy of the earlier application whose priority has been claimed.

   ☐ translation of the earlier application whose priority has been claimed.

2. ☒ This report has b en established as if no priority had been claimed du to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 7-17.

because:

☒ the said international application, or the said claims Nos. 7-17 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☒ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:

see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☒ all parts.

☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3,7-15,17,20-24,26-28
	No:	Claims	1-2, 4-6, 16,18-19
Inventive step (IS)	Yes:	Claims	
	No:	Claims	3,7-15,17,2-24,26-28
Industrial applicability (IA)	Yes:	Claims	1-6, 18-24, 26-28 completely; 7-17 partially
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by th description, ar made:

see separat sh et

Reference is made to the following documents cited in the Search Report:

D1: NORONHA A. ET AL.: 'Triple helices containing arabinonucleotides in the third (Hoogsteen) strand: effects of inverted stereochemistry at the 2'-position of the sugar moiety.' NUCLEIC ACIDS RES 1998 JUN 1;26(11):2665-71, cited in the application

D2: AOYAGI, M. ET AL.: 'Effects of 2'-alpha- and 2'-beta-bromo-2'-deoxyadenosine on oligonucleotide hybridization and nuclease stability.' BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 6, 1996, pages 1573-1576

D3: GIANNARIS P.A. ET AL: 'Hybridization properties of oligoarabinonucleotides.' CANADIAN JOURNAL OF CHEMISTRY, (1994) 72/3 (909-918), cited in the application

D4: NORONHA, A. & DAMHA, M.: 'Hybridization properties of arabinonucleic acids (ANA), influence of stereochemistry at 2' on the stability of double and triple helices' JOURNAL OF BIOMOLECULAR STRUCTURE & DYNAMICS, vol. 14, June 1997 (1997-06), pages 805-806

D5: KOIS ET AL: Nucleosides & Nucleotides **12** (1993) 1093 *; cited in the application

D6: WILDS CJ. ET AL.: 'Duplex recognition by oligonucleotides containing 2'-deoxy-2'-fluoro-D-arabinose and 2'-deoxy-2'-fluoro-D-ribose. Intermolecular 2'-OH-phosphate contacts versus sugar puckering in the stabilization of triple-helical complexes.' BIOCONJUG CHEM 1999 MAR-APR;10(2):299-305

D7: DAMHA M.J. ET AL: 'Hybrids of RNA and arabinonucleic acids (ANA and 2'F-ANA) are substrates of ribonuclease H.' JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, (16 DEC 1998) 120/49 (12976-12977).

D8: Lima & Crooke: Biochemistry **36** (1997) 390-398 *; cited in the application

D9: WO 93 10820

D10: WO 90 03370

* The documents D5 and D8 have not been cited in the international search report. Copies of the documents have not been supplied as they are known to the applicant.

Re Item I

Basis of the opinion

1. Sequence listing pages 1/4-4/4 (published with WO 99/67378) have been taken into account.

2. With respect to the new set of claims filed 29.08.2000 it is noted that for the phrase "substituted at 2' position of the sugar ring other than with hydroxyl" in relation to triple helix formation neither a basis has been provided nor can be identified in the originally filed application (claims 1, 8 and 18). Newly filed claims 1, 8 and 18 are therefore not taken into account and replaced by claims 1, 8, 18 of the set of claims filed 20.04.2000.

3. With respect to claims 2, 9 and 19 no basis is also found for the exclusion of hydroxyl in the oligonucleotide (except for 2'F-ANA). In view of these non-acceptable amendments claims 1-20 as filed in april of this year are taken as the claimed subject-matter together with the later filed claims 21-30 (but not acceptable claims 25 and 29-30; see below).

4. A basis for claims 11 and 25 having the new wording "(iv) cleavage of target RNA by RNAse H" is also not found; this reasoning applies also to claims 17 and 30 (concerning the amendment, in the second line of the claims, of ANA oligonucleotide into ANA nucleotide and/or the back reference to claim 8).

5. Claim 29: a basis cannot be found for the newly introduced subject-matter.

Re Item II

Priority

6. The contents of the priority document CA 2,241,361 (filing date 19.06.98; henceforth designated P1) differs considerably from the present international application (see e.g. the "Summary of the Invention" in the application pages 17-19 and in P1, page 15; with respect to the oligonucleotides with the formula specified it is noted that in P1 the furanose ring only contains oxygen; see e.g. claims 2-3 and 20): thus at least present claims 1-5 lack a right of priority.

Claims 1 and 2 of P1 correspond (although not in detail) with the subject-matter of claims 6 and 7 of the international application. Claim 2 of P1 refers to hybrid DNA (purine)/RNA (pyrimidine) and claim 7 as filed to DNA/RNA in general: the hybrid DNA/RNA in general is therefore also not considered to be entitled to the priority date of P1.

Present claim 16 (invention iii) is not considered to be entitled to the right of priority and documents **D6** and **D7** are therefore also available for citation against the subject-matter of invention iii.

Introduction

7. Claim 1 of the present application concerns an oligonucleotide consisting of arabinose sugars hybridizing to either I). Single stranded RNA (to induce Rnase H activity; see also claim 7), or ii). Duplex DNA/DNA or DNA/RNA (to form a triple helical complex; see also claim 8).

8. Arabinose sugar containing oligonucleotides (arabinonucleic acid, or ANA) are already known from the prior art, as well as their property to form triple helices (see D1), to hybridize with complementary DNA or RNA (see D3, Table 3 and D4) and to influence the stability towards nuclease (see D2, Figure 2).

9. Claim 16 is a method involving DNA (nucleic acid) enzymes comprising an oligonucleotide analogue (comprising e.g. an arabinofuranose).

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

10. For the assessment of present claims 7-17 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such

a compound for the manufacture of a medicament for a new medical treatment.

Claims 7-17 (as far as in vivo methods are involved) relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item IV
Lack of unity of invention

11. The present International Preliminary Examining Authority identifies three independent inventions in the present application as follows:

i. Claims 7 and 15 completely, and claims 1-6, 9-14 and 17-20 partially: concerning the hybridization to a single stranded RNA;

ii. Claim 8 completely, and claims 1-6, 9-14 and 17-20 partially: concerning the hybridization to a duplex DNA/DNA or DNA/RNA to form a triple helical complex;

iii. Claim 16: concerning a method carried out by a DNA (nucleic acid) enzyme.

12. With respect to the reasons for the observation of non-unity the following is noted:

A single general inventive concept (referred to in Rule 13 PCT and the PCT Preliminary Examination Guidelines Ch.III, 7) is not recognisable in the absence of a common, special technical feature: independent claims 7, 8 and 16 have only in common the fact that they refer to ANA which is already well known from the prior art. Claims 7, 8 and 16 are not referring to 2'F-ANA only, thus e.g. a binding affinity cannot be taken as the unifying feature.

13. The Applicant decided to pay the additional fees (under protest) so that all inventions are examined.

Re Item V
Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

14. **Claims 1-2, 4-6 and 18-19:** these claims refer to known products: reference is

made to all prior art concerning ANA's and further modified ANA's (see e.g. D5 and above "Introduction").Therefore, the present application does not satisfy the criterion set forth in Article 33(2) PCT because the subject-matter of said claims is not new in respect of prior art as defined in the regulations (Rule 64(1)(3) PCT).

Claims 3 and 20: these claims specify 2 F substitutions in the 2' stereoisomer position of D-arabinose/ribose, in which case the anomaly in the sugar ring is lost. No prior art is available disclosing the oligonucleotide of claims 3 and 20, however, this oligo is considered to be one of the obvious alternatives available to the skilled person (please see e.g. D6 in combination with D5, page 1094, paragraph above "Experimental Part" referring to 2'-F-ribo-T). Thus, claims 3 and 20 are neither inventive (Article 33(3) PCT) nor are they fully supported by the description as their synthesis does not appear to have been disclosed.

Invention I. Claims 7 and 15 and depending claims.

15. Methods for cleaving single stranded (ss) RNA by first hybridizing to an (antisense, modified) oligonucleotide and followed by cleaving of the hybridized RNA by RNase H is known from the prior art (see D8 and also D7, reference 5). It appears that no prior art has disclosed the use of antisense ANA's for this use, hower it is considered that in view of the known method for other modified oligonucleotides (such as oligonucleotide phosphorothioates) in combination with the teaching of D5 (see e.g. the introduction and conclusion) the subject-matter of these claims is obvious to the skilled person (Article 33(3) PCT). It is additionally noted that claims 7 and 15 do **not** refer to (fully modified) 2'F-ANA oligomer.

In particular it is noted that the replacement of ribose by arabinose in oligomers would clearly not impose any particular problems: see in addition D2-D4 (in particular D3 mentioning that the inversion of stereochemistry at the C2' of ribonucleotides does not have a negative effect on interaction with natural DNA or RNA sequences), D9 (in particular page 25 lines 6 and 30, page 70, first full paragraph and claims 45, 52 and 95-98) and D10 (claims 20 and 23).

Claims 7 and 15 have as characterising features "oligonucleotide consisting essentially of arabinose sugars" and "induce RNase H activity". The cleavage of

the hybridized ss RNA (i.e. of the duplex) depends both on the affinity of the binding of the two strands and the type of RNase H. In the present case the characterization is only in general terms: it is not clear how many sugar rings in the oligonucleotide have the arabinose or ribose configuration, as well as which type of Rnase H (mammalian, viral, bacterial?) is to be used. It appears that reference should be made to uniformly sugar-modified arabinose-oligonucleotides.

It is further noted that the technical problem of invention I is clearly different from the technical problem of invention ii, as in invention i the duplex binding affinity should still support RNase H activity, while in invention ii the highest stability of the triple helical complex is to be achieved.

16. Depending claims: these claims only specify further obvious structural elements of the ANA's: the definition of these further structural elements (including e.g. the definition of Y as Br) is within the reach of the person skilled in the art without the need of inventive skill. Consequently, the subject-matter of these depending claims also lacks an inventive step.

With respect to claim 10 it is noted that it is not demonstrated that the claimed oligonucleotide indeed solves the technical problem.

Invention ii. Claim 8 and depending claims.

17. Methods to inhibit DNA replication/transcription by hybridizing (modified) oligonucleotides to duplex DNA/DNA or DNA/RNA to form a triple helix are known from the prior art: claim 107 of D9 specifies the inhibition of expression of the protein in a cell by introducing an oligomer and permitting to form a triplex with the DNA or RNA. D1 has already been mentioned in the introduction supra.

Therefore, it is considered that the disclosure of D9 in combination with the teaching of D1 renders the subject-matter of **claim 8** obvious to the skilled person.

It is noted that the conclusion in D1 was that, in order to design sequence selective oligonucleotides which interact with ds nucleic acids, the composition of the backbone is to be considered (ANA was shown to form triple-helical

complexes only with duplex DNA and hybrid DNA(Pu):RNA(Py). In present claim 8 neither special reference is e.g. made to this composition, nor to only F-ANA compounds

18. Depending claims: these claims only specify obvious structural elements of the ANA's.

Invention iii.

19. It is noted that the search examiner mentioned that the subject-matter of claim 16 (previously claim 15) has not been searched as the chemical reaction nor the meaning of DNA enzyme are defined in the application. At present, an opinion is however given, in view of the fact that the essential feature of the invention appears to depend on the composition of claim 2.
Claim 16 on file appears to relate to a chemical synthesis method catalyzed by a DNA enzyme inwhich the composition of claim 2 is used.

The composition of claim 2 is known from the prior art : the hybridization properties of ANA have been described (see also references 7-9 of D7) and also of 2'F-ANA some of the properties like **enzymic hydrolysis** and stability of oligonucleotide duplexes have been described (see D7, e.g. bottom of page 1105). It is therefore considered that the subject-matter of claim 16 does not fulfill the requirements of PCT (Art.33(2)) , as it is not novel over the disclosure of D7.

If claim 16 refers to an enzymic activity of the oligonucleotides of claim 2 per se, than support is missing in the application.

Re Item VIII
Certain observations on the international application

20. In conjunction with the above observation with respect to the lack of unity of invention, it is noted that Article 6 of the PCT requires that all independent claims contain the essential technical feature(s) to define the invention.

At present the special and essential technical feature of the independent claims of the three inventions is not recognisable.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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C12N 15/11, C07H 21/00, A61K 31/70 // C07H 19/09, 19/19

A1

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2,241,361 19 June 1998 (19.06.98) CA

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(74) Agents: COTE, France; Swabey Ogilvy Renault , Suite 1600, 1981 McGill College Avenue, Montréal, Québec H3A 2Y3 (CA) et al.

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Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: ANTISENSE OLIGONUCLEOTIDE CONSTRUCTS BASED ON β-ARABINOFURANOSE AND ITS ANALOGUES

(57) Abstract

The present invention relates to modified oligonucleotide therapeutic agents to selectively prevent gene transcription and expression in a sequence-specific manner. In particular, this invention relates to the selective inhibition of protein biosynthesis via antisense strategy using oligonucleotides constructed from arabinonucleotide or modified arabinonucleotide residues. More particularly this invention relates to the use of antisense oligonucleotides having arabinose sugars to hybridize to complementary RNA such as cellular messenger RNA, viral RNA, etc.

FOR THE PURPOSES OF INFORMATION ONLY

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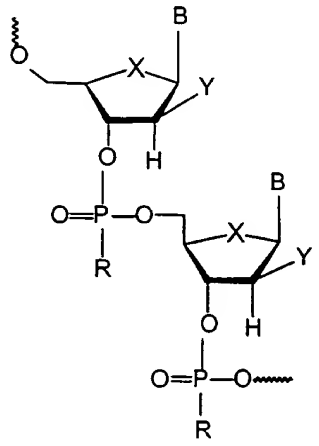
TM	Turkmenistan
TR	Turkey
TT	Trinidad and Tobago
UA	Ukraine
UG	Uganda
US	United States of America
UZ	Uzbekistan
VN	Viet Nam
YU	Yugoslavia
ZW	Zimbabwe

WHAT IS CLAIMED IS:

1. A therapeutic composition to selectively prevent gene transcription and expression in a sequence-specific manner in a host; which comprises an effective amount of at least one selected from the group consisting of an oligonucleotide consisting essentially of arabinose sugars hybridizing to a single stranded RNA to induce RNase H activity; an oligonucleotide consisting essentially of arabinose sugars hybridizing to duplex DNA/DNA or DNA/RNA to form a triple helical complex, in association with a pharmaceutically acceptable carrier.

2. The therapeutic composition of claim 1, wherein said oligonucleotide has the formula:



wherein,

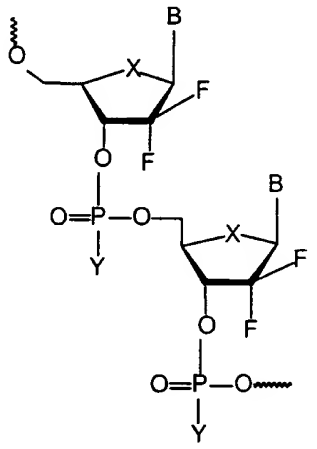
B is selected from the group consisting of adenine, guanine, uracil, thymine, cytosine, inosine, and 5-methylcytosine;

Y at the 2′ position of the sugar ring is selected from the group consisting of a halogen (fluorine, chlorine, bromine, iodine), hydroxyl, alkyl, alkylhalide (e.g., $-CH_2F$), alkylsulfhydryl ($-SCH_3$) allyl, amino, aryl, alkoxy, and azido;

R at the internucleotide phosphate linkage is selected from the group consisting of oxygen, sulfur, methyl, amino, alkylamino, dialkylamino (the alkyl group having one to about 20 carbon atoms), methoxy, and ethoxy; and

X at the furanose ring (position 4′) is selected from the group consisting of oxygen, sulfur, and methylene (CH_2).

3. The therapeutic composition of claim 1, wherein said oligonucleotide has the formula:



wherein,

B is selected from the group consisting of adenine, guanine, uracil, thymine, cytosine, inosine, 5-methylcytosine;

Y at the internucleotide phosphate linkage is selected from the group consisting of oxygen, sulfur, methyl,

amino, alkylamino, dialkylamino (the alkyl group having one to about 20 carbon atoms), methoxy, and ethoxy; and

X at the furanose ring (position 4') is selected from the group consisting of oxygen, sulfur, and methylene (CH_2).

4. The therapeutic composition of claim 1 or 2, wherein said RNA is complementary RNA.

5. The therapeutic composition of claim 4, wherein said complementary RNA is cellular mRNA or viral RNA.

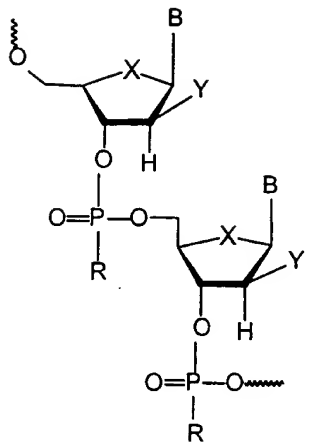
6. A method for cleaving single stranded RNA, which comprises the steps of:

a) hybridizing in a sequence specific manner an oligonucleotide consisting essentially of arabinose sugars to a single stranded RNA to induce RNase H activity; and

b) allowing said induced RNase H to cleave said hybridized single stranded RNA.

7. A method to inhibit DNA replication and/or DNA transcription, which comprises hybridizing in a sequence specific manner an oligonucleotide consisting essentially of arabinose sugars to duplex DNA/DNA or DNA/RNA to form a triple helical complex; thereby inhibiting DNA replication and/or DNA transcription.

8. The method of claim 6 or 7, wherein said oligonucleotide has the formula:



wherein,

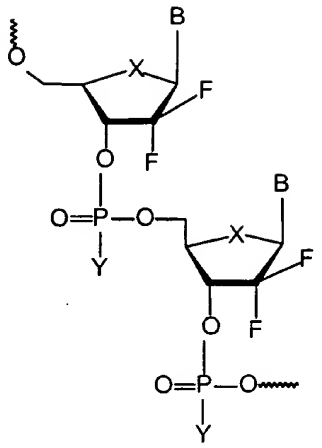
B is selected from the group consisting of adenine, guanine, uracil, thymine, cytosine, inosine, and 5-methylcytosine;

Y at the 2′ position of the sugar ring is selected from the group consisting of a halogen (fluorine, chlorine, bromine, iodine), hydroxyl, alkyl, alkylhalide (e.g., $-CH_2F$), alkylsulfhydryl ($-SCH_3$) allyl, amino, aryl, alkoxy, and azido;

R at the internucleotide phosphate linkage is selected from the group consisting of oxygen, sulfur, methyl, amino, alkylamino, dialkylamino (the alkyl group having one to about 20 carbon atoms), methoxy, and ethoxy; and

X at the furanose ring (position 4′) is selected from the group consisting of oxygen, sulfur, and methylene (CH_2).

9. The method of claim 6 or 7, wherein said oligonucleotide is



wherein,

B is selected from the group consisting of adenine, guanine, uracil, thymine, cytosine, inosine, 5-methylcytosine;

Y at the internucleotide phosphate linkage is selected from the group consisting of oxygen, sulfur, methyl, amino, alkylamino, dialkylamino (the alkyl group having one to about 20 carbon atoms), methoxy, and ethoxy; and

X at the furanose ring (position 4') is selected from the group consisting of oxygen, sulfur, and methylene (CH_2).

10. The method of claim 6 or 7 wherein said oligonucleotide is chemically modified at least at one site with a ligand or a pharmacological agent to enhance at least one of: (i) permeability of said oligonucleotide into cells, (ii) nuclease stability, or (iii) binding strength of hybridization to complementary sequences.

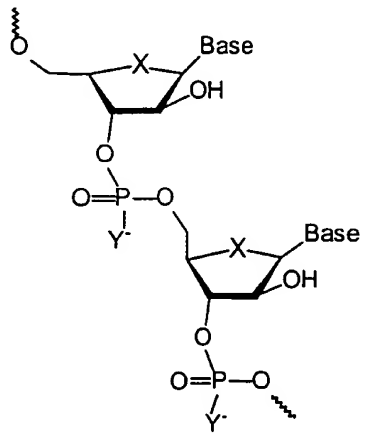
11. The method of claim 10, wherein the ligand is a cell surface receptor, at least one L-sugar residue, a

3'-to-3' linked nucleotide, at least one 2-O-methyl-D-ribose sugar.

12. The method of claim 6, wherein said RNA is complementary RNA.

13. The method of claim 12, wherein said complementary RNA is cellular mRNA or viral RNA.

14. A method for selectively cleaving RNA, which comprises selectively hybridizing an oligonucleotide consisting essentially of β-D-arabinofuranose nucleotide units to RNA without hybridizing to single stranded DNA in a sequence specific manner, said oligonucleotide has the formula:



wherein said oligonucleotide has a mixed base composition;

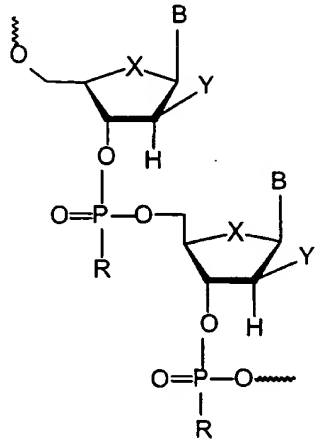
wherein,

B is selected from the group consisting of adenine, guanine, uracil, thymine, cytosine, inosine, and 5-methylcytosine;

Y at the internucleotide phosphate linkage is selected from the group consisting of oxygen, sulfur, methyl, amino, alkylamino, dialkylamino (the alkyl group having one to about 20 carbon atoms), methoxy, and ethoxy; and

X at the furanose ring (position 4') is selected from the group consisting of oxygen, sulfur, and methylene (CH_2).

15. A method of catalyzing chemical reactions carried out by DNA enzymes, which comprises using at least one oligonucleotide selected from the group consisting of β-D-arabinofuranose, 2-deoxy-2-fluoro-β-D-arabinose, and 2-deoxy-2,2-difluoro-β-D-ribose units to catalyze catalytic DNA chemical reactions, wherein said oligonucleotide has the formula:



wherein the oligomer has a mixed base composition;

wherein,

B is selected from the group consisting of adenine, guanine, uracil, thymine, cytosine, inosine, and 5-methylcytosine;

Y at the 2' position of the sugar ring is selected from the group consisting of a halogen (fluorine, chlorine, bromine, iodine), hydroxyl, alkyl, alkylhalide ($-CH_2F$), alkylsulfhydryl ($-SCH_3$), allyl, amino, aryl, alkoxy, and azido;

R at the internucleotide phosphate linkage is selected from the group consisting of oxygen, sulfur, methyl, amino, alkylamino, dialkylamino (the alkyl group having one to about 20 carbon atoms), methoxy, and ethoxy; and

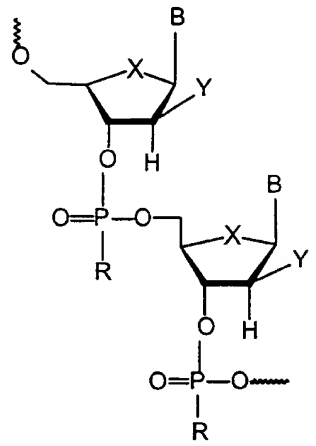
X at the furanose ring (position 4') is selected from the group consisting of oxygen, sulfur, and methylene (CH_2).

16. The method of claim 6 or 7 wherein said oligonucleotide is a chimera of at least one ANA oligonucleotide and at least one 2'F ANA oligonucleotide to enhance at least one of: (i) permeability of said oligonucleotide into cells, (ii) nuclease stability, or (iii) binding strength of hybridization to complementary sequences.

17. An oligonucleotide for selectively preventing gene transcription and expression in a sequence-specific manner in a host; which comprises an oligonucleotide consisting essentially of arabinose sugars hybridizing to a single stranded RNA to induce RNase H activity; an oligonucleotide consisting essentially of arabinose sugars hybridizing to duplex DNA/DNA or DNA/RNA

to form a triple helical complex; and at least one 2-O-methyl-D-ribose sugar at 3', 5' or both terminus of said oligonucleotide.

18. The oligonucleotide of claim 17, wherein said oligonucleotide has the formula:



wherein,

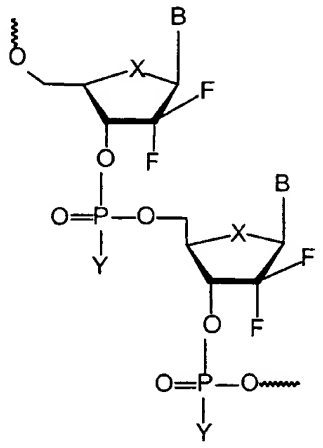
B is selected from the group consisting of adenine, guanine, uracil, thymine, cytosine, inosine, and 5-methylcytosine;

Y at the 2' position of the sugar ring is selected from the group consisting of a halogen (fluorine, chlorine, bromine, iodine), hydroxyl, alkyl, alkylhalide (e.g., $-CH_2F$), allyl, amino, aryl, alkoxy, and azido;

R at the internucleotide phosphate linkage is selected from the group consisting of oxygen, sulfur, methyl, amino, alkylamino, dialkylamino (the alkyl group having one to about 20 carbon atoms), methoxy, and ethoxy; and

X at the furanose ring (position 4') is selected from the group consisting of oxygen, sulfur, and methylene (CH_2).

19. The oligonucleotide of claim 17, wherein said oligonucleotide has the formula:



wherein,

B is selected from the group consisting of adenine, guanine, uracil, thymine, cytosine, inosine, 5-methylcytosine;

Y at the internucleotide phosphate linkage is selected from the group consisting of oxygen, sulfur, methyl, amino, alkylamino, dialkylamino (the alkyl group having one to about 20 carbon atoms), methoxy, and ethoxy; and

X at the furanose ring (position 4') is selected from the group consisting of oxygen, sulfur, and methylene (CH_2).

SEQUENCE LISTING

<110> McGILL UNIVERSITY
DAMHA, Massad, José
PARNIAK, Michael, A.
NORONHA, Anne, M.
WILDS, Christopher
BORKOW, Gadi
ARION, Dominique

<120> ANTISENSE OLIGONUCLEOTIDE CONSTRUCTS
BASED ON BETA-ARABINOFURANOSE AND ITS ANALOGUES

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INTERNATIONAL SE H REPORT

Inter[illegible]nal Application No
PCT/CA 99/00571

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/11 C07H21/00 A61K31/70 //C07H19/09,C07H19/19

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07H C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NORONHA A. ET AL.: "Triple helices containing arabinonucleotides in the third (Hoogsteen) strand: effects of inverted stereochemistry at the 2'-position of the sugar moiety." NUCLEIC ACIDS RES 1998 JUN 1;26(11):2665-71, XP002119321 cited in the application the whole document ---	7,8
X	AOYAGI, M. ET AL.: "Effects of 2'-alpha- and 2'-beta-bromo-2'-deoxyadenosine on oligonucleotide hybridization and nuclease stability." BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 6, 1996, pages 1573-1576, XP004175756 ISSN: 0960-894X the whole document ---	7,8

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 October 1999	02/11/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Andres, S

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 10820 A (GILEAD SCIENCES INC) 10 June 1993 (1993-06-10) page 25 -page 28 page 38, line 21 -page 40, line 6 page 70, line 7 -page 71, line 17	1,4,5,7, 10-13
X	WO 90 03370 A (MICROPROBE CORP) 5 April 1990 (1990-04-05) page 4, line 9 -page 6, line 35 claims 16-26	1,4-7
A	GIANNARIS P.A. ET AL: "Hybridization properties of oligoarabinonucleotides." CANADIAN JOURNAL OF CHEMISTRY, (1994) 72/3 (909-918), XP002119322 cited in the application the whole document	1-14, 16-19
A	SANGHVI, Y. & COOK, D.: "Carbohydrates: synthetic methods and applications in antisense therapeutics" ACS SYMPOSIUM SERIES, vol. 580, 13 March 1994 (1994-03-13), pages 1-22, XP002119323 ISSN: 0097-6156 cited in the application the whole document	1-14, 16-19
A	ALTMANN, K.-H. ET AL.: "Novel chemistry" STEIN, C.A. & KRIEG, A.M. 'APPLIED ANTISENSE OLIGONUCLEOTIDE TECHNOLOGY'. WILEY-LISS, NEW YORK, US;1998, pages 73-107, XP002119324 the whole document	1-14, 16-19
A	NORONHA, A. & DAMHA, M.: "Hybridization properties of arabinonucleic acids (ANA), influence of stereochemistry at 2' on the stability of double and triple helices" JOURNAL OF BIOMOLECULAR STRUCTURE & DYNAMICS, vol. 14, June 1997 (1997-06), pages 805-806, XP002119325 abstract	1-14,16, 17
A	XODO LE. ET AL.: "Effect of 5-methylcytosine on the structure and stability of DNA. Formation of triple-stranded concatenamers by overlapping oligonucleotides." J BIOMOL STRUCT DYN 1994 FEB;11(4):703-20, XP002119326	

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	FLANAGAN, M. ET AL.: "Effects of oligonucleotide length, mismatches and mRNA levels on C-5 propyne modified antisense potency" NUCLEIC ACIDS RESEARCH., vol. 24, 1996, pages 2936-2941, XP002119327 ISSN: 0305-1048 cited in the application	
P,X	WILDS CJ. ET AL.: "Duplex recognition by oligonucleotides containing 2'-deoxy-2'-fluoro-D-arabinose and 2'-deoxy-2'-fluoro-D-ribose. Intermolecular 2'-OH-phosphate contacts versus sugar puckering in the stabilization of triple-helical complexes." BIOCONJUG CHEM 1999 MAR-APR;10(2):299-305, XP002119328 the whole document	7,8
P,X	DAMHA M.J. ET AL: "Hybrids of RNA and arabinonucleic acids (ANA and 2'F-ANA) are substrates of ribonuclease H." JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, (16 DEC 1998) 120/49 (12976-12977)., XP002119329 the whole document	6,8,14

INTERNATIONAL SEARCH REPORT

rnational application No.
PCT/CA 99/ 00571

Box I Observations where certain claims w r found uns archabl (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 6 to 14 (as far as in vivo methods are concerned) are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 15
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

The wording of claim 15 '... catalyzing a chemical reaction carried out by DNA enzymes...' does not allow a meaningfull search to be carried out. Indeed, neither the chemical reaction, nor the meaning of DNA enzyme are defined in the application

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 15

The wording of claim 15 '... catalyzing a chemical reaction carried out by DNA enzymes ...' does not allow a meaningfull search to be carried out. Indeed, neither the chemical reaction, nor the meaning of DNA enzyme are defined in the application.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interr[illegible]nal Application No
PCT/CA 99/00571

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9310820 A	10-06-1993	US 5484908 A	16-01-1996
		AU 3222793 A	28-06-1993
		AU 679508 B	03-07-1997
		AU 6345394 A	15-09-1994
		CA 2122365 A	10-06-1993
		DE 637965 T	14-12-1995
		EP 0637965 A	15-02-1995
		JP 7501527 T	16-02-1995
		US 5830653 A	03-11-1998
		US 5645985 A	08-07-1997
WO 9003370 A	05-04-1990	CA 1338379 A	11-06-1996
		US 5824796 A	20-10-1998
		US 5849482 A	15-12-1998

PATENT COOPERATION TREA

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
1770-206PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/CA 99/ 00571	17/06/1999	19/06/1998
Applicant		
McGILL UNIVERSITY et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[X] contained in the international application in written form.

[X] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. –

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 99/00571

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 6 to 14 (as far as in vivo methods are concerned) are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 15
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

The wording of claim 15 '... catalyzing a chemical reaction carried out by DNA enzymes...' does not allow a meaningfull search to be carried out. Indeed, neither the chemical reaction, nor the meaning of DNA enzyme are defined in the application

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 15

The wording of claim 15 '... catalyzing a chemical reaction carried out by DNA enzymes ...' does not allow a meaningfull search to be carried out. Indeed, neither the chemical reaction, nor the meaning of DNA enzyme are defined in the application.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 99/00571

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/11 C07H21/00 A61K31/70 //C07H19/09,C07H19/19

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07H C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NORONHA A. ET AL.: "Triple helices containing arabinonucleotides in the third (Hoogsteen) strand: effects of inverted stereochemistry at the 2'-position of the sugar moiety." NUCLEIC ACIDS RES 1998 JUN 1;26(11):2665-71, XP002119321 cited in the application the whole document ---	7,8
X	AOYAGI, M. ET AL.: "Effects of 2'-alpha- and 2'-beta-bromo-2'-deoxyadenosine on oligonucleotide hybridization and nuclease stability." BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 6, 1996, pages 1573-1576, XP004175756 ISSN: 0960-894X the whole document ---	7,8

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 October 1999	02/11/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Andres, S

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 10820 A (GILEAD SCIENCES INC) 10 June 1993 (1993-06-10) page 25 -page 28 page 38, line 21 -page 40, line 6 page 70, line 7 -page 71, line 17	1,4,5,7, 10-13
X	WO 90 03370 A (MICROPROBE CORP) 5 April 1990 (1990-04-05) page 4, line 9 -page 6, line 35 claims 16-26	1,4-7
A	GIANNARIS P.A. ET AL: "Hybridization properties of oligoarabinonucleotides." CANADIAN JOURNAL OF CHEMISTRY, (1994) 72/3 (909-918), XP002119322 cited in the application the whole document	1-14, 16-19
A	SANGHVI, Y. & COOK, D.: "Carbohydrates: synthetic methods and applications in antisense therapeutics" ACS SYMPOSIUM SERIES, vol. 580, 13 March 1994 (1994-03-13), pages 1-22, XP002119323 ISSN: 0097-6156 cited in the application the whole document	1-14, 16-19
A	ALTMANN, K.-H. ET AL.: "Novel chemistry" STEIN, C.A. & KRIEG, A.M. 'APPLIED ANTISENSE OLIGONUCLEOTIDE TECHNOLOGY'. WILEY-LISS, NEW YORK, US;1998, pages 73-107, XP002119324 the whole document	1-14, 16-19
A	NORONHA, A. & DAMHA, M.: "Hybridization properties of arabinonucleic acids (ANA), influence of stereochemistry at 2' on the stability of double and triple helices" JOURNAL OF BIOMOLECULAR STRUCTURE & DYNAMICS, vol. 14, June 1997 (1997-06), pages 805-806, XP002119325 abstract	1-14,16, 17
A	XODO LE. ET AL.: "Effect of 5-methylcytosine on the structure and stability of DNA. Formation of triple-stranded concatenamers by overlapping oligonucleotides." J BIOMOL STRUCT DYN 1994 FEB;11(4):703-20, XP002119326	

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FLANAGAN, M. ET AL.: "Effects of oligonucleotide length, mismatches and mRNA levels on C-5 propyne modified antisense potency" NUCLEIC ACIDS RESEARCH., vol. 24, 1996, pages 2936-2941, XP002119327 ISSN: 0305-1048 cited in the application	
P,X	WILDS CJ. ET AL.: "Duplex recognition by oligonucleotides containing 2'-deoxy-2'-fluoro-D-arabinose and 2'-deoxy-2'-fluoro-D-ribose. Intermolecular 2'-OH-phosphate contacts versus sugar puckering in the stabilization of triple-helical complexes." BIOCONJUG CHEM 1999 MAR-APR;10(2):299-305, XP002119328 the whole document	7,8
P,X	DAMHA M.J. ET AL: "Hybrids of RNA and arabinonucleic acids (ANA and 2'F-ANA) are substrates of ribonuclease H." JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, (16 DEC 1998) 120/49 (12976-12977)., XP002119329 the whole document	6,8,14

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INTERNATIONAL SEARCH REPORT

mation on patent family members

International Application No
PCT/CA 99/00571

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9310820 A	10-06-1993	US 5484908 A	16-01-1996
		AU 3222793 A	28-06-1993
		AU 679508 B	03-07-1997
		AU 6345394 A	15-09-1994
		CA 2122365 A	10-06-1993
		DE 637965 T	14-12-1995
		EP 0637965 A	15-02-1995
		JP 7501527 T	16-02-1995
		US 5830653 A	03-11-1998
		US 5645985 A	08-07-1997
WO 9003370 A	05-04-1990	CA 1338379 A	11-06-1996
		US 5824796 A	20-10-1998
		US 5849482 A	15-12-1998